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AP1-08039: Clinical Development of a Cell Therapy for Diabetes

SCORES AND RECOMMENDATIONS

Score: 91
GWG Recommendation: Recommended for funding
CIRM Recommendation: Fund

Module 2
Score: <65
GWG Recommendation: Not recommended for funding

Module 3
Score: 72
GWG Recommendation: Tier2, Moderate quality or no consensus
CIRM Recommendation: Fund

Module 4
Score: <65
GWG Recommendation: Not recommended for funding

Public Abstract (provided by applicant)
We are developing a stem cell-derived replacement cell therapy for insulin-requiring diabetes. Through a process known as directed differentiation, embryonic stem cells are turned into pancreatic cells in the laboratory. The pancreatic cells are loaded into a delivery device, which is essentially a small envelope made with a semi-permeable membrane, not unlike a flat tea bag. When the cells in the device (combination product) are implanted under the skin, they become pancreatic endocrine cells, including insulin-producing beta cells that respond to elevated blood glucose by releasing insulin in a physiologic manner. The prototype combination product has been tested in hundreds of animals, is routinely curative in a mouse model of chemically-induced diabetes, and has been shown to be safe in several animal studies. Moreover, the delivery device has been shown to protect cells from a recipient's immune system. The Team has received valuable feedback from the FDA, and we plan to launch the first clinical test of our therapeutic candidate in patients with diabetes in 2014. This first clinical trial will utilize the prototype to establish safety in humans, and determine the dosing range that might provide benefit to patients with diabetes.

The current application is to fund additional clinical research, and associated product development activity, that will (1) ensure the first trial is executed in a most informative and timely fashion, (2) accelerate the pace at which information is collected on how the product works in humans – testing various formats, and in different types of patients – and (3) substantially increase the likelihood that the most appropriate format and patient population is selected for a definitive "Phase 3" clinical trial. A Phase 3 trial serves as the basis for an application to the FDA to obtain a license to market the product. In this way, CIRM Accelerated Development Pathway designation of the project will substantially increase the probability that, and pace at which, this product concept becomes a real treatment available to the millions of patients in need.

Statement of Benefit to California (provided by applicant)
Diabetes mellitus currently afflicts approximately 370 million people worldwide, with projections of over 550 million by the year 2030 (sources: World Health Organization; International Diabetes Federation). In the year 2000 there were approximately 2 million cases of diabetes in California (source: Diabetes Control Program, California Department of Health Services). Further, the disease disproportionately affects certain minority groups and the elderly. Despite the use of insulin and advances in its delivery, the human cost of diabetes is underscored by the financial costs to society: tens of billions of dollars each year in California alone. The primary cause of type 1 diabetes, and contributing significantly to type 2 diabetes as well, is the loss of insulin-producing pancreatic beta cells. The CIRM Diabetes Disease Team Project is developing an innovative beta cell replacement therapy for insulin-requiring diabetes. If

successful, the therapy will go beyond insulin function, and will perform the full array of normal beta cell functions, including responding in a more physiological manner than manual or mechanized insulin self-administration. Because they will be more physiological, the replacement cells could reduce the long-term effects of diabetes. Moreover, the cell therapy will alleviate patients of the constant monitoring of blood glucose, painful insulin injections, and the ever-present risk of overdosing with insulin. For these reasons, it is possible that the product could transform the diabetes treatment landscape dramatically and even replace pharmaceutical insulin in the market. This product will be available in California first, through clinical testing, and if approved by the FDA for commercial production, will eventually help hundreds of thousands of Californians with diabetes. The product will substantially increase quality of life for patients and their families, while significantly reducing the health care burden in the state. The proposed project will employ Californian doctors and scientists, and success will prove highly noteworthy for the state. Lastly, once commercially marketed, the product will yield additional jobs in manufacturing, sales, and related industries, and generate revenue for California. Given the market need and the clear feasibility, the product could become the most significant stem cell-based medical treatment of the coming decade, and that will be a tremendous achievement for California, its taxpayers, and CIRM.

REVIEW SUMMARY

The therapeutic candidate under development for the Parent Award and the subject of this application is a combination product comprising an hESC-derived cell therapy delivered in a macroencapsulation device for the treatment of Type 1 Diabetes Mellitus (T1DM). The Parent Award includes the IND submission and a Phase 1/2, first in human (FIH) clinical trial. For this application, four modules of activities were proposed. Module 1 was requested to introduce additional functional studies into the Phase 1/2 FIH clinical trial funded under the Parent Award and to add a 3-year follow up period to that clinical trial. Also proposed in Module 1, is the development of an improved device that would allow more flexibility for dosing. In Module 2, the applicants requested funding for a parallel Phase 2 clinical trial in a subpopulation of T1DM patients in whom the applicants predict that effects of the therapeutic may be rapidly detected and offer significant benefit over current therapies, which could facilitate more rapid Regulatory approval. Module 3 would fund activities to enable rapid transition to pivotal studies, including process scale-up of cell production, the development of a larger capacity device, and the bridging studies required to integrate these modifications. Module 4 would fund preclinical work and then a clinical study in another patient subgroup to address whether immunosuppressive medication could improve product efficacy.

As an update to the GWG recommendations, the FDA approved the IND for the Phase 1/2 FIH clinical trial in August.

Clinical Competitiveness and Impact of the Proposed Therapy

- This therapeutic candidate has the potential to significantly impact, and potentially transform, the treatment for T1DM. If the combination product proves successful, reviewers projected that it would have advantages over existing therapies and insulin delivery systems.

- The idea of pursuing administration of the therapeutic in a subset of patients, as proposed in Module 2, was viewed positively in terms of potentially advancing the product to market. However, the reviewers expressed that the proposed clinical trial in Module 2 should follow, and be informed by, the Phase 1/2 FIH trial in the general T1DM target population (the Parent Award and Module 1).

Strength of the Development Program

- The preclinical package suggests a good safety profile with promising efficacy data. However, the team is still awaiting Regulatory feedback that will determine whether the non-clinical safety and device testing are sufficient, and when they may be permitted to proceed with the clinical trial (update since the time of the GWG review, the FDA approved the IND of the phase 1/2 FIH clinical trial in August).

- Reviewers described the clinical Development Plan to the end of Phase 2 as well developed and thorough.

- Reviewers agreed that the appropriate patient population had been proposed for the Phase 1/2 FIH trial, and that the trial is designed with clear clinical endpoints and outcome measures that will broadly inform the Development Plan.

- While the team is planning for success, they acknowledge that there is a risk to the program that the therapeutic will not perform as expected from the preclinical experience. Reviewers were encouraged that the team had considered mitigation strategies (such as the activities proposed in Module 1 to allow scaling the cell dose administered) and noted that the team's plans allow them to remain flexible and responsive as clinical data become available.

- While reviewers appreciated the benefits of considering additional patient groups in the Development Plan, as was proposed in Modules 2 and 4, it was widely expressed that it was critical to first get robust clinical proof of mechanism and proof of concept information from the Phase 1/2 FIH clinical trial prior to any consideration of administration of the therapeutic to other patient subsets.

Qualifications of Development Team

- The team and their consultants are well qualified, with a strong track record in stem cell product development and bioengineering.

- Reviewers described the team as having extensive regulatory experience, strong and qualified project management, and clinical operations personnel with excellent experience in the target disease and in the cell therapy arena.

- The team has breadth of experience in academia, industry, manufacturing and clinical trials and this group has a demonstrated track record of working together.

Progress on Parent Award and Effective Program Leadership
- Development challenges have delayed progress on the Parent Award, but the team has effectively managed these delays in a timely manner and have stayed close to their original timeline in the Parent Award for IND filing.

- The team is on schedule to file their IND in Q3/2014 to support initiation of the Phase 1/2 FIH clinical trial (update since the time of the GWG review, the FDA approved the IND of the Phase 1/2 FIH clinical trial in August).

- The device testing and development activities were described as well designed and consistent with regulatory expectations.

Relevance of the Therapeutic to Regenerative Medicine
- The relevance to regenerative medicine is considered a "tremendous" strength of the project. A demonstration of success with this stem cell-based product would provide a huge leap forward for regenerative medicine.

- The project is based on innovative science that utilizes hESC-derived cells in a clinical indication with a testable mechanism of action and cutting edge delivery technology.

- The delivery component of this product could have broad implications as a platform technology for the field in that it could potentially be used to deliver other stem cell-based therapeutics for a wide range of clinical conditions.

Proposed Activities for Acceleration of the Development Program
- The expansion of the Phase 1/2 FIH trial, as proposed in Module 1, is well justified, focused and integral to achieving clinical proof of concept. Specifically, the proposed additional functional study could identify whether the product acts through multiple regulatory mechanisms important for glucose control; if so, this would present a clear advantage over standard insulin replacement therapy.

- The proposed Module 3 activities in manufacturing, process improvements and scale-up were felt to be necessary for commercialization and for accelerating the product's path to market, with a caveat that its impact in terms of accelerating the development program will be dependent on how this activity is impacted, and informed, by results of the Phase 1/2 FIH clinical study (i.e. in determining the appropriate device size/cell dose). The proposed bridging clinical study could provide proof of concept for a commercializable product in 2017, although some reviewers thought that timeline was optimistic. In addition, the reviewers noted the open label extension study proposed in Module 3 is appropriate.

- The proposed clinical trials in Modules 2 and 4 were viewed as non-essential and premature, due to a prerequisite for sufficient proof of concept data from the Phase 1/2 FIH trial, and a lack of preclinical data, respectively. Given the novelty of the device design and therapy, it seems likely that unexpected findings could arise from the first clinical trial that would be essential to informing the next trial(s). Therefore, activities proposed in Modules 2 and 4 were not thought to be accelerating to the Development Program at this time.

Feasibility of Proposed Activities for Acceleration of the Development Program
- Activities proposed in Module 1 are feasible and would bolster the Phase 1/2 FIH trial funded under the Parent Award to provide information regarding clinical proof of mechanism and proof of concept in a relatively short time frame. However, some reviewers considered the timelines provided (start date and time to obtaining safety and efficacy data) for the Phase 1/2 FIH clinical trial to be overly optimistic.

- Activities proposed in Module 3 are feasible and have a high probability of success given the applicant's track record.

- The reviewers assessed the feasibility of the clinical trial proposed in Module 2 as highly dependent on the results in the Phase 1/2 FIH trial. It will likely be more difficult to enroll the patient subgroup proposed for the clinical trial proposed in Module 2 and long-term follow up of those patients could pose feasibility challenges.

Module 1
- The expansion of the clinical trial proposed in Module 1 is related to achieving the key milestone of a FIH clinical trial. Reviewers

commented that the information gained by addition of the functional study and the proposed longer follow-up period to the Phase 1/2 FIH trial would both inform follow-on trials and accelerate the overall Development Program. Initiating steps to expand the dosing capability of the device in a timely manner was viewed as a valuable strategy to help mitigate future programmatic delays.

- Progressive device scale up will be critical for commercialization and initiating this work along the timeline proposed in Module 1 would accelerate the path to market, provided that it is well informed and reflects ongoing developments during the Phase 1/2 FIH clinical trial.

- Activities proposed in Module 1 were viewed as critical to support progress to patients and guide the direction of the entire clinical Development Program.

Module 3
- The activities proposed in Module 3 are to develop and manufacture a large capacity cell device that can then be tested in preclinical models and bridged into use for future clinical trials. Reviewers assessed these activities, as well as the proposed work to support scale up of cell manufacturing and incorporation of cryopreservation methods into the manufacturing process, as necessary steps to support development for larger clinical trials and future commercialization of the product. Success in the Phase 1/2 FIH clinical trial will necessitate the activities proposed in Module 3.

- Reviewers expressed that initiating the activities proposed in Module 3 in parallel with conducting the Phase 1/2 FIH study would accelerate the overall development program and prevent possible long interruptions in clinical delivery to patients. However, some reviewers expressed that it may be prudent to approach the proposed cell manufacturing and device scale up activities in Module 3 in a staggered fashion. They proposed that cell manufacturing process improvements and development work for the larger capacity device could be initiated, but that the team await interim results from the Phase 1/2 FIH trial before proceeding with bridging activities.

Conflicts:
John Wagner

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